Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research

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ABSTRACT

Psychiatric disorders are linked to a variety of biological, psychological, and contextual causes and consequences. Laboratory studies have elucidated the importance of several key physiological and behavioral biomarkers in the study of psychiatric disorders, but much less is known about the role of these biomarkers in naturalistic settings. These gaps are largely driven by methodological barriers to assessing biomarker data rapidly, reliably, and frequently outside the clinic or laboratory. Mobile health (mHealth) tools offer new opportunities to study relevant biomarkers in concert with other types of data (e.g., self-reports, global positioning system data). This review provides an overview on the state of this emerging field and describes examples from the literature where mHealth tools have been used to measure a wide array of biomarkers in the context of psychiatric functioning (e.g., psychological stress, anxiety, autism, substance use). We also outline advantages and special considerations for incorporating mHealth tools for remote biomarker measurement into studies of psychiatric illness and treatment and identify several specific opportunities for expanding this promising methodology. Integrating mHealth tools into this area may dramatically improve psychiatric science and facilitate highly personalized clinical care of psychiatric disorders.

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The purpose of this review is to describe opportunities to improve measurement of biomarkers via mobile health (mHealth) approaches in an effort to expand our understanding of mental health, psychiatric disorders, and substance use to improve clinical services. First, we describe the current context and rationale for this type of work. We then highlight illustrative examples of current work being conducted in the area of remote biomarker acquisition and analysis using mobile sensing devices for select areas of psychiatric clinical research. We also discuss how mHealth approaches to biomarker acquisition has potential to improve research on psychopathology and intervention outcomes. Finally, we describe strategies and opportunities for clinical researchers to accelerate advances in the field by integrating mHealth tools for biomarker acquisition into studies of psychiatric illness and treatment.

1. Biomarkers in psychiatric clinical research

Psychiatric disorders are common (Kessler et al., 2005) and a leading risk factor for poor quality of life worldwide (Whiteford et al., 2013). Psychiatric disorders are linked to a variety of biological, psychological, and contextual causes and consequences. Central to moving the mental health field forward is better understanding of complex mechanisms underlying psychiatric disorders and further optimizing treatment strategies to each patient's needs, referred to recently as precision medicine (Insel, 2014; Office of the Press Secretary, January 30, 2015). Several biological (i.e., genetic, physiological, endocrine, neural) markers of risk, resilience, and treatment response have been identified recently in relation to psychiatric disorders (Schmidt et al., 2011; Singh and Rose, 2009; Volkow et al., 2015). Less is known about the role or impact of these biomarkers in naturalistic settings, largely due to

methodological barriers to assessing such variables rapidly, reliably, and validly outside of a laboratory setting. One promising avenue for addressing this gap extends from the field of mobile health (mHealth). mHealth refers to the use of a diverse set of tools and resources—often mobile and wireless communication devices—designed to deliver and improve healthcare services, outcomes, information and research (Labrique et al., 2013; Nilsen et al., 2012; Vital Wave Consulting, 2009). Innovative mHealth technologies that blend remote acquisition of biomarker data with other types of remotely acquired patient data (e.g., self-reported mood, global positioning system location data, exposure to stress triggers) may improve dramatically psychiatric science and clinical care.

Here, we have adopted a broad definition of what constitutes a biomarker. This definition is based on the recommendation put forth by The Biomarkers Consortium (Biomarkers Definitions Working Group et al., 2001), a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (NIH): "Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention." We have expanded the definition somewhat to consider "behavioral biomarkers" that may serve as a proxy for underlying biological processes related to or indicative of psychiatric disorders. For example, behavioral biomarkers may include data from such sources as accelerometry, actigraphy, paralinguistic monitoring, and many others (e.g., (Saeb et al., 2015). The collection of such behavioral and physiological biomarkers via digital tools has also been dubbed "digital biomarkers" (Wang et al., 2016). Our goal is not to make stark distinctions between biological and behavioral data, but rather to broadly examine a wide array of biomarkers that may be collected remotely to better understand and treat psychiatric disorders.

2. mHealth has improved real-time measurement of clinically relevant data

Most mHealth research in psychiatry has focused on using short message service (SMS) text messaging or web-enabled applications to measure self-reported symptoms or functioning; measuring and linking contextual factors (e.g., time, location) to self-reported symptoms or behaviors; or delivering interventions via mobile devices, typically based on user self-report or environmental factors. The advent of mobile phones and personal digital assistants brought new opportunities to gather psychosocial, contextual, and self-reported behavioral data in the field via electronic daily diaries and real-time experience sampling or ecological momentary assessment (EMA) (Shiffman et al., 2008). These approaches automate several aspects of data collection and afford more rigorous tracking of timing and context than conventional paper-and-pencil techniques, which are vulnerable to recall bias and other errors (Kaplan and Stone, 2013). The potential reach and scalability of these approaches has boomed alongside growing ubiquity of personal mobile phones. National data indicate very high rates of mobile phone ownership (90% overall, over 97% among adults aged 18–49) (Pew Research Center, 2014), including smartphone ownership (64% overall, over 80% among adults aged 18–49) (Pew Research Center, 2015). These figures are reliably higher among racial/ethnic minority groups, and are similar across education level, household income, and geographic location, underscoring the wide potential reach of mobile devices for clinical research.

Advances in mHealth have led to innovative work uncovering the causes of psychiatric problems, including substance use disorders (SUDs), and afforded a more fine-grained, ecologically valid analysis of how risk and vulnerability factors interact than were previously possible in laboratory studies (Kaplan and Stone, 2013).

For example, in the field of smoking research, EMA has been applied in nearly 300 published studies to provide a remarkably detailed picture of the in-the-moment mechanisms and processes by which contextual and psychological factors interact and contribute to craving and relapse (Schüz et al., 2015), which has used mostly one-way data collection methods. Many new mHealth technologies extend beyond EMA and leverage the functionality and convenience of personal mobile devices to promote behavior change (Fox and Duggan, 2012; Kaplan and Stone, 2013; Nilsen et al., 2012). For instance, adaptive ecological momentary interventions move beyond one-way data collection to two-way data streams (Heron and Smyth, 2010). Recent work has begun to evaluate the utility of mHealth in the treatment and prevention of psychiatric disorders (Luxton et al., 2011; Price et al., 2014; Reger et al., 2013) and SUDs (Marsch and Ben-Zeev, 2012; Marsch, 2012; Marsch et al., 2014; Marsch and Dallery, 2012; Sloan et al., 2011). Although many studies are underway, findings from early studies highlight the promise of this "revolution" (Sloan et al., 2011) in extending the reach and effectiveness of existing evidence-based treatments (EBTs) by promoting patient engagement, facilitating the treatment process, and sustaining post-treatment gains (Clough and Casey, 2011a; b; Luxton et al., 2012; Marsch et al., 2014; Marsch and Dallery, 2012; McTavish et al., 2012; Price et al., 2014). Arguments also have been made for the use of mobile devices to collect physiological data in both research and clinical contexts to improve our understanding of the etiological processes and mechanisms underlying treatment effects (Kaplan and Stone, 2013; Stopczynski et al., 2014); however, relatively few research programs in psychiatry have thus far reported findings related to mHealth biomarker collection.

3. The appeal of mHealth for remote biomarker acquisition to advance psychiatric research

Careful measurement of biomarker data alongside other indicators and correlates of psychopathology and substance use aligns with strategic priorities of public health agencies. For example, the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative prioritizes consideration of the causes of psychopathology and how they interact with environmental factors across development or change in response to treatment (Cuthbert and Insel, 2013). Per the RDoC initiative, constructs should be measured dimensionally across multiple units of analysis, including genes, neural circuits, physiology, behavior, and self-report. Historically, clinical researchers have been limited in their ability to measure such factors simultaneously, in real-time, repeatedly, and in patients' daily ecologies. The acquisition of biomarkers in research and clinical settings often requires substantial time and effort for participants, patients, and staff, in addition to the costs incurred with transportation, specialized training for personnel, and the expensive equipment often required for sample storage, processing, and analysis. Collecting biomarker data in naturalistic settings via conventional methods required participants to collect and store specimens (e.g., saliva, urine) at specific times to be sent into a laboratory for processing or otherwise gather and record readings (e.g., measure blood pressure and write down results) and other pertinent information (e.g., day, time, context) manually for subsequent analysis. These complicated procedures carry heightened opportunities for error and data loss.

When the target measurement frequency is several times daily or weekly, it may be unrealistic and overly burdensome for patients to visit a clinic or laboratory to provide samples or specimens. Among patients suffering from severe psychiatric disorders, the self-tracking of behavior and symptoms to indicate stability is often times too difficult to maintain for long periods of time. A recent

review discussed and advocated for continuous and unobtrusive sensing to detect and prevent worsening of mental illness symptoms (Matthews et al., 2014). Tools that facilitate user-friendly remote acquisition of biomarkers and other data in participants' daily ecologies—ideally with point-of-contact processing and analysis and low user burden—are therefore highly desirable. Until recently, technological limitations prevented use of similar strategies for reliable remote sampling and analysis of biological data. Hence, many unanswered questions persist about whether associations between biological processes and psychiatric problems observed in the laboratory generalize to real-world settings or clinical care.

Several promising and powerful new mHealth tools permit remote acquisition of biomarker data for clinical or research purposes. Most entail mobile phone applications that interface with built-in or external sensors to integrate subjective and objective indices of behavior, physiological functioning, and environmental context, and many of the biosensors are increasingly inexpensive and widely available. Data often can be automatically logged and stored through user-friendly portals. These tools provide objective measures of clinically useful information, such as changes in targeted physiological functioning over the course of treatment, and powerful point-of-use decision support to guide intervention selection (Shetty and Yamaguchi, 2010). Such data can promote effective disease self-management and the ability of clinicians to make treatment decisions based on data collected between in-person clinic visits.

Psychiatry lags behind other areas of medicine (e.g., endocrinology, cardiology) with regard to published empirical studies that report validation efforts and data from applied studies of mobile biomarker measurement. However, an emerging set of technologies and methodologies illustrates how such approaches could be applied to the field. These tools support simultaneous integrated acquisition of biomarker data, self-reported ratings of variables like distress and craving, and automatically obtained data such as time of day and geographical coordinates to contextualize environmental factors—hence, it is possible to obtain phenomenally rich data efficiently and cost effectively, in some cases with a single device already owned by many participants or patients.

4. Method

The authors conducted an extensive literature search through January 2016 using several electronic databases, including PubMed, PsycINFO, and Google Scholar. The following keywords (and permutations thereof) were used in our search: mobile health, mhealth, psychiatry, psychology, stress, mental health, mental illness, psychiatric disorders, substance use disorders, addiction, alcohol, tobacco, technology, biomarkers, biochemical, sensors, biosensors, physiology, mobile phones, and smartphones. We also explored articles cited in the reference sections of relevant articles, book chapters, and review papers. Studies were included if they involved measurement of biomarkers via mHealth tools (smartphone, mobile biosensor device) in the context of psychiatric populations or phenomena. There were no exclusion criteria based on sample size or participant demographics. The examples cited below represent the current status of biomarker collection within psychiatric research, though we recognize that many other new technologies and devices are currently being developed and evaluated. Given the rapidly evolving nature of this area, innovative examples of remote biomarker acquisition that had been reported in the published literature were chosen for discussion in the current review. We could not dedicate full attention to technologies in development or those that have not yet been extended for use in psychiatric research specifically or evaluated in published studies,

but we recognize that those technologies represent exciting future resources and avenues of inquiry. These technologies have primarily been applied to clinical problems related to stress, anxiety, attention-deficit/hyperactivity disorder, autism, substance use, and sleep problems, but other examples are also highlighted.

5. Review of examples from the literature

5.1. Mobile biosensing of stress and anxiety

There are several examples from the literature demonstrating the use of mobile biosensors to measure autonomic nervous system (ANS) functioning, psychological stress, and anxiety. Although the role of stress and ANS clearly extends beyond psychiatric disorders, these factors are strongly implicated in a range of mental health problems. Plarre et al. (2011) used the Bluetooth-enabled Auto-Sense wearable sensor suite (Ertin et al., 2011; Hovsepian et al., 2015) to measure electrocardiogram (ECG) readings, skin conductance, skin temperature, ambient temperature, and lung volume in young adults during multiple lab-based stress induction tasks (n = 21), as well during as a field-based EMA procedure (n = 17) (Plarre et al., 2011). Although some difficulties with data loss were reported, the investigators demonstrated strong correspondence between sensor-acquired values and self-reported stress ratings and concluded that it is possible to use remote sensors to predict differences in self-reported perceived stress within and between people based on physiological data collected via remote biosensors. In a related study, Sun et al. (2012) collected wireless ECG using a chest strap sensor and galvanic skin response (GSR) in adults using finger sensors and a wrist cuff (Sun et al., 2012). Biomarker data collected in the laboratory study was used to successfully differentiate stress and non-stress conditions, and illustrated how physiological data collected using the portable, wireless sensors could be collected and transmitted reliably to a server via Bluetooth. The Empatica system is another example of a wearable multi-sensor device (similar to a wristwatch) to collect multiple ANS indices as part of the affective computing movement. Empatica and earlier models has been used to characterize and discriminate stress responses in healthy adults (Garbarino et al., 2014; Ming-Zher et al., 2010; Picard, 2015). Collectively, these projects illustrate trends in the growing "affective computing" movement, which has clear links to psychiatric science and clinical care.

Low-cost mobile devices also have been developed that rapidly analyze stress markers in saliva samples. Salivary alpha amylase (sAA) is a validated biomarker of sympathetic nervous system functioning. Yamaguchi, Shetty, and colleagues developed and validated a sAA biosensor that uses an optical platform and disposable colorimetric test strips to detect and quantify sAA in less than 1 min (Shetty et al., 2011; Yamaguchi et al., 2006). This noninvasive approach requires very small saliva volumes and eliminates the need for expensive storage and processing equipment. With regard to the feasibility of these devices for clinical research, healthy adult male participants (n = 54) were directed to complete scheduled (3 times per day, 2 days) remote sAA sampling using the portable biosensors and rate their concurrent momentary subjective distress (Robles et al., 2011). The investigators found that participants in that study were over 90% compliant with the saliva sampling procedures (i.e., providing a saliva sample within 60 min of a scheduled sampling time), supporting the feasibility of deploying the portable sensor in naturalistic settings. As more portable biosensors are developed that index other stress biomarkers detectable in saliva, such as cortisol (Yamaguchi et al., 2013), the potential to fold these tools into clinical practice and research will grow.

Another innovative approach to remote measurement of ANS

activity is to capture heart rate variability, pulse, and breathing rate simultaneously via digital camera. McDuff et al. (2014) demonstrated that changes in stress-related physiological functioning can be detected remotely using facial videos captured with an inexpensive digital camera (McDuff et al., 2014). Findings from that pilot study were validated against contact sensors worn by participants during rest and during a cognitive stress condition, and the remote video parameters correctly classified participants in the rest versus stress conditions 85% of the time. Other research by the same team has demonstrated feasibility of estimating respiration and heart rates through passive data collection via built-in smartphone sensors (e.g., accelerometer) as people engage in typical activities such as sitting, standing, or using the phone (Hernandez et al., 2015). Using a software system called StressSense, researchers leveraged built-in smartphone microphones to capture young adult users' vocal characteristics that were then analyzed to accurately classify stress in naturalistic settings (Lu et al., 2012). With further refinement, these strategies could be particularly useful in gathering non-invasive measures of stress and anxiety—compared to an individual's baseline—across a range of settings without requiring specialized sensors. Such data could be valuable for clinicians or researchers interested in surveillance of ANS functioning and predicting or identifying changes in stress that could be used to alert users to use coping skills in real-time.

5.2. Mobile biosensing in cigarette smoking

Most mobile biomarker research in the area of smoking cessation has focused on the measurement of carbon monoxide (CO) in the breath. Breath CO is a non-invasive biological test of recent smoking, but typically degrades quickly (half life 2—8 h) (SRNT Subcommittee on Biochemical Verification, 2002). Studies attempting to circumvent the burden placed on patients and staff to obtain frequent biochemical measures have provided CO monitors to study participants so that they can record themselves leaving a breath CO sample that is then quantified and uploaded to a secure study website (Dallery and Glenn, 2005; Dallery et al., 2007; Glenn and Dallery, 2007). This system has been extended to use with rural smokers (Stoops et al., 2009) and adolescents (Reynolds et al., 2008), and has been implemented on a mobile platform (Hertzberg et al., 2013). Also, the hardware used to collect biomarkers of smoking is changing to support remote collection. A recent study described the validation of a prototype mobile-based breath CO monitor that communicates directly with a smartphone (Meredith et al., 2014).

Advancing beyond CO monitoring to detect smoking, several other systems are being explored that use sensing technology to capture smoking in an unobtrusive manner. Respitrace® is a device that measures chest expansion during smoking episodes (St Charles et al., 2009). *mPuff* is a system that measures respiration patterns through chest expansion, but can be worn in the field and directly transmits information to a mobile device (Ali et al., 2012). A newer system, *puffMarker*, is designed to detect instances of smoking (most notably, lapses to smoking following abstinence) using respiration and arm movement sensors (Saleheen et al., 2015). This system makes use of the wireless Autosense sensor suite (Ertin et al., 2011). Preliminary work also is being conducted with inertial sensors that detect movement of the arm and wrist indicating smoking (Raiff et al., 2014; Varkey et al., 2012), as well as system that combines respiration measures with hand gestures (Sazonov et al., 2013). Additionally, there are a number of mHealth applications that are being explored pertaining to the mobile sensing of smoking as a means of delivering treatment, which have great potential to improve abstinence outcomes among smokers (McClernon and Choudhury, 2013).

5.3. Mobile biosensing in alcohol use disorders

Similar technologies to those used to detect smoking have been extended to study and treat alcohol use disorders. Several different means of alcohol detection exist in the literature, with more in development. For example, one study made use of commercially available alcohol breathalyzers, which participants used while recording their samples via a mobile device (Alessi and Petry, 2013). Another study used transdermal alcohol sensors (i.e., Secure Continuous Remote Alcohol Monitoring [SCRAM]) to monitor drinking (Barnett et al., 2011). Transdermal alcohol sensors that measure alcohol excreted in perspiration have been used within the criminal justice system for several years and are only recently being utilized within research and clinical care contexts and hold great potential for this area (Barnett, 2015). The sensors come with several limitations, however, including a longer latency for alcohol consumption to be detected via perspiration (Leffingwell et al., 2012).

5.4. Mobile biosensing in illicit substance use

Biosensor technologies are also being used to detect use of illicit substances, such as opiates and cocaine. For example, a multi-sensor wristband designed to collect continuous electrodermal activity, skin temperature, and acceleration has been evaluated in detection of intravenous drug use in an emergency department setting (opiates) and in a brief, 4-h field test (cocaine) (Carreiro et al., 2015). Findings from that small pilot test indicated that biomarker data—especially electrodermal activity—could feasibly be used to identify episodes of IV drug use, though more data are needed regarding the reliability and validity of observed patterns in larger samples and in less controlled environments. Moreover, the investigators reported having difficulty enrolling participants into the field test due to privacy concerns endorsed by potential participants about having their location and behavior known by law enforcement officials.

The AutoSense sensor suite described above has also been evaluated as a strategy for detecting cocaine intake in adult active drug users across residential laboratory (N = 9) and community-based settings (N = 42) (Hossain et al., 2014). The investigators built a predictive model for identifying patterns of nervous system activity measured via ECG that corresponded to cocaine use events. The authors reported significant challenges with collecting a sufficient number of drug use events with good quality ECG data; however, the final model yielded a100% true positive rate in identifying cocaine use events and a false positive rate of approximately 1 event per day. Additional studies in this vein are needed that focus on other drugs of abuse and that integrate other types of biomarker and sensor-derived data.

5.5. Mobile biosensing in autism

Similar mHealth approaches to measuring and monitoring autonomic functioning have been developed to predict risk for outbursts and other symptoms among people with autism, as well as to help children with autism increase their awareness and understanding of emotional responses to stimuli in their environments (Gay et al., 2013; Leijdekkers et al., 2013). These approaches blend physiological arousal data gathered via wristworn sensors and chest bands with facial expression data captured using built-in cameras. A related line of research has leveraged sensors (cameras, accelerometers) to generate multimodal behavioral profiles that can then be used to supplement the traditional sources of data available to clinicians for diagnosis of autism and other developmental disorders (Rehg et al., 2013, 2014). In one example of this

"behavioral imaging" approach, data from wearable cameras have been used to model and detect abnormalities in child gaze and eye contact—two symptoms of autism—during a structured interaction with an adult (Ye et al., 2015). Such technologies may also be used in naturalistic settings to extend the reach of assessment procedures and to guide just-in-time interventions, such as social or behavioral coaching. In a similar vein, the promising "Autism and Beyond" mobile application, launched through Apple Inc.'s ResearchKit initiative, involves using the built-in front-facing camera of the iPhone to capture images of users' facial expressions in response to standardized stimuli (https://autismandbeyond. researchkit.duke.edu/). These images are analyzed using emotion recognition algorithms to identify youth who are possibly at risk for autism and other developmental disorders. Research on the validity and utility of this approach is currently underway in a large-scale trial.

5.6. Mobile biosensing in mood disorders

Whereas mobile apps designed to capture self-reported mood ratings or deliver intervention packages for mood problems like depression or bipolar disorder are increasingly common, relatively few mHealth projects have focused specifically on measuring biomarkers associated with mood disorders. But some promising approaches are being evaluated. For example, researchers have analyzed combinations of self-reported data with sensor derived phone usage (Faurholt-Jepsen et al., 2015), mobility, and physical activity (Gruenerbl et al., 2014; Osmani et al., 2013). Other lab-based work has measured paralinguistic characteristics of speech (pitch, rate, etc.) collected using a microphone a to predict individual differences in depressive and manic symptoms in patients with bipolar disorder (Vanello et al., 2012), and similar techniques have been applied to detect patterns of behavioral cycling observed in bipolar disorder using smartphone microphones to capture vocal characteristics(Abdullah et al., 2016). Related work has demonstrated feasibility of predicting depressive symptoms from environmental context and activity data collected via an array of built-in sensors including GPS, accelerometers, and ambient light sensors (Burns et al., 2011; Saeb et al., 2015), which can then be used to deliver targeted in-the-moment interventions.

5.7. Mobile biosensing in attention-deficit/hyperactivity disorder (ADHD)

Mobile biosensing research on ADHD and its treatment is somewhat more advanced than in other areas of psychiatry. Several review articles have been published in the last six years that illustrate the current state of the field and future directions. The majority of the work in the remote acquisition of biomarkers in ADHD has used actigraphy to detect activity and sleep quality in this population. Wrist-worn motion actigraphs and sensors designed to measure heart rate, GSR, and other physiological indices can be used to gather information about arousal, alertness, and hyper-/hypoactivity, as well as information about sleep patterns. One meta-analytic review compared objective measures of sleep to subjective measures among children with ADHD (Cortese et al., 2009), while the second focused on actigraphy to detect methylphenidate (vs. placebo) treatment response in randomized trials (De Crescenzo et al., 2015). In those studies, actigraphy data were used as naturalistic observations of hyperactivity symptoms. Finally, a recent article made use of actigraphy readings of activity, sleep, and circadian rhythms to differentiate ADHD from bipolar disorder in a pediatric population (Faedda et al., 2016).

A recent review argued for the importance of biomarker identification and validation in the diagnosis and treatment of ADHD

and autism spectrum disorder, with a focus on electrophysiological biomarkers (Jeste et al., 2015). While the acquisition of biomarkers discussed in that review primarily occurs in the clinic or laboratory, it is easy to envision the extension of this work to include remote acquisition for clinical research. As mobile, ambulatory electrophysiology readings and more sensitive actigraphy devices and algorithms improve, greater strides will follow in efforts to improve our understanding and ability to treat and monitor ADHD effectively.

6. Discussion

6.1. Future applications of mHealth biomarker collection in psychiatric research

To date, mHealth methods have been used to study a small fraction of psychiatric phenomena and biomarkers. One potential avenue to build on this progress would be to integrate remote biomarker collection strategies like those described above into research on a broader range of disorders and constructs and in large samples. To illustrate, acute threat (a construct in the NIMH RDoC Negative Valence Systems domain) may be operationalized using physiological measures of startle, heart rate, skin conductance, blood pressure, eye tracking, and pupillometry (National Institute of Mental Health, 2011)—virtually all of these biomarkers of acute stress and fear have been or could plausibly be assessed using mobile technologies. Given that the majority of work in this area has involved adult samples, there may also be benefit in expanding mHealth biomarker research into youth populations to better characterize the development of psychiatric problems.

Data from multiple sources could be analyzed to understand *in vivo* interactions among various determinants of substance use and psychopathology in etiological or epidemiological research, or processed immediately to inform just-in-time interventions based on predetermined parameters. With the use of mobile technologies to capture and integrate a wealth of data at several levels on these complex disorders, we have the opportunity to longitudinally monitor these conditions to provide the best possible care and interventions in-between office visits. This also provides the opportunity to proactively intervene during periods of relapse or condition severity, rather than the typical retroactive responses to acute issues. Given that telemedicine models, by definition, involve remote contact between patients and providers, remotely acquired biomarker data may be a natural fit in that context.

As technologies designed to measure relevant psychiatric biomarkers are expanded and refined, quantitative physiological outputs may be used as objective indicators of treatment response progress over the course an intervention. Clinical trials, in particular, may benefit from the inclusion of mHealth approaches to biomarker collection. Recently, experts have recommended an integral role for mHealth and eHealth strategies toward improvement of clinical research methods (Baker et al., 2014; Riley et al., 2013). For instance, mHealth-based strategies for biomarker measurement can be used as validation checks for medication adherence by measuring drug metabolites or biochemical targets known to be influenced by medication. Biomarker measurement is not only pertinent to pharmacological treatments, however. Theoretically and empirically pertinent biomarkers can also be measured to test or illustrate response to psychosocial and behavioral interventions. For example, in-the-moment measurement and analysis of biomarkers related to the stress response (cortisol, heart rate, skin conductance) during an exposure or relaxation exercise could provide important information about how treatments for anxiety disorders work and whether participants/patients are able to engage in similar levels of intervention independently compared to

sessions with a therapist present. The same types of measurements could be used to assess within-subjects change over the course of treatment to characterize concordance versus discordance among biomarkers, clinician observation, and self-reported symptoms, as well as between-subjects comparisons across experimental treatment conditions. In this way, these tools and techniques also may provide critical information about what mechanisms might moderate or mediate treatment effects.

Although the focus of this review is on assessment, the capacity for remote collection and integration of rich physiological data associated with stress and anxiety has also been applied to psychiatric *intervention*. For example, drawing from the stress and anxiety literature, Repetto et al. (2013) used finger sensors to measure heart rate and electrodermal activity (GSR) among adults with generalized anxiety disorder (GAD) (Repetto et al., 2013). The sensors wirelessly transmitted data to a tablet computer to deliver biofeedback in real-time during exposure exercises, and remotely acquired physiological functioning was found to be a sensitive index of intervention effects. Sano et al. (2015) evaluated a platform ("HealthAware") for assessing and providing tailored feedback on stress and related behavioral health concerns (sleep, diet, and exercise) using a combination of web-based surveys and the Fitbit® wearable sensor (Sano et al., 2015). In their two-week pilot study (n = 30 adults), the investigators demonstrated the acceptability of the approach, though challenges with promoting behavior change were noted. Rather than using external heart rate sensors, Gregoski et al. have developed and validated a strategy for using the built-in video cameras that are ubiquitous among modern smartphones as reflective photoplethysmographs to measure heart rate (Gregoski et al., 2011, 2012, 2013). The photoplethysmograph has been integrated with a breathing awareness meditation protocol into a stress management mobile app called Tension Tamer®. Preliminary evidence from pre-hypertensive adults supports the utility of measuring heart rate and providing real-time physiological data to users during meditation exercises in one mHealth platform. Findings from these studies and others in different areas of psychiatric research illustrate the feasibility of delivering tele-mental health interventions that incorporate remotely collected physiological data (i.e., for biofeedback, clinical research studies) with other intervention components and self-reported data on mental health and wellbeing.

Given that biomarker data acquired via mobile sensors is readily—if not automatically—digitized, it would also be possible to merge into or cross-reference existing databases, such as a person's electronic medical record (EMR) or population-level norms, to broaden the range of available information. In fact, two health systems have recently developed methods to integrate data captured from Apple HealthKit into Epic EMRs (Comstock, 2014). Despite this potential, the integration of mHealth data into EMRs carries significant ethical, practical, legal, and clinical challenges that warrant careful consideration and additional research before widespread implementation can occur. For instance, computing systems need to be developed that can accommodate and efficiently process the enormous amount of data that may be gathered if remote biomarker collection becomes more common, and policies pertaining to privacy and liability—especially around high-risk or illicit behaviors that may be inferred from ongoing biometric data collection—still need to be sorted out. Still, early work in health data integration has huge potential for psychiatric research and clinical decision-making and dramatically increasing the scale of data collection for psychiatric clinical research.

Despite the promise and potential of mHealth integration into remote biomarker acquisition, this area of work is not without its weaknesses and limitations. Among the illustrative studies in selected disorders discussed in the current review, there are several limitations to consider. Many of the technology systems described above are expensive, bulky, and require a substantial amount of work on the part of the study participant that may not be realistic for long periods of monitoring or among patients not engaged in a research study. Also, many of the studies mentioned were intended as proof of concept or validation work for technology systems, leading to small sample sizes and limited impact. This is not surprising given this is a new and rapidly growing research area, where the focus to date has largely been on technology development and early-stage trials. Even with such small sample sizes, the amount of data captured from these studies was immense, and in several cases, research staff and investigators were responsible for verifying values, cleaning data, developing and refining algorithms, and troubleshooting device issues—tasks that will be automated in future iterations. Importantly, engagement and sustained use of these technology systems are key issues that will determine their adoption. The value the user perceives and the relevance of the system must be considered in the early stages of programming and development. These barriers and challenges bring to the light questions regarding the scalability of such systems for remote biomarker acquisition, which is essential to consider as the development and refinement of technology occurs.

6.2. Challenges, considerations, and recommendations for psychiatric clinical researchers

Best practice guidelines for incorporating mHealth strategies—and, more specifically, remote collection of biomarker marker data—into psychiatry research are evolving alongside the rapidly changing technological landscape. Here, we address some key considerations and challenges facing this emerging area of study and offer recommendations for investigators who may wish to incorporate mHealth biomarker measurement approaches into their research. This list is not exhaustive, but highlights common questions and reservations to using mHealth in studies involving biomarker collection:

6.2.1. Consider the necessity and appropriateness of mHealth tools

Many researchers are tempted by the appeal of integrating mHealth approaches into their work. Simply because a technology appears to be innovative does not mean that it will improve the execution of study procedures or impact of findings. *Recommendations:* It is vital to consider whether adding mHealth techniques will help answer the research question and improve the accuracy, feasibility, generalizability, cost-effectiveness, convenience, efficacy, and sustainability of the study protocol or results. In many cases, technology *can* improve many of the criteria listed above, but careful consideration is recommended prior to embarking on the substantial effort required to integrate mobile technologies into research studies. As with any new assessment tool, it is important that mHealth biosensors are subjected to rigorous validation studies (e.g., laboratory-based comparisons to existing gold-standard approaches) prior to using the devices in the field while also considering the importance of efficient scientific progress and clinical application.

6.2.2. Understand industry and multidisciplinary partner relationships, intellectual property, and commercialization

Many biosensor devices described here, and others in development or commercially available, were developed in whole or in part by private companies. Psychiatric researchers rarely receive training in intellectual property and technology commercialization. Many mHealth applications developed by private industry do not conform to evidence-based information or guidelines (Abroms et al., 2013; Abroms et al., 2011; Jacobs et al., 2014), and few

Table 1
Studies involving remote biomarker acquisition to address psychiatric clinical problems.

Authors (Year)	Biomarker	Collection method	Hardware	Timing of data collection	Study sample	Adh.	Conclusions	Barriers or Challenges
Smoking								
Dallery and Glenn (2005)	Breath carbon monoxide (CO)	Video recorded CO samples on a computer; emailed to study team	CO monitor, webcam, laptop	2×/day (8 h apart) for 4 wks	Adult smokers (n = 4)	95%	Feasible to collect CO remotely and deliver incentives	Equipment was loaned to participants; drove to participant homes to set up
Dallery et al. (2007)	Breath CO	Video recorded CO samples on a computer; emailed to study team	CO monitor, webcam, laptop	2×/day (8 h apart) for 4 wks	Adult heavy smokers (n = 20)	98%	Feasible to collect CO remotely and deliver incentives	Providing equipment, cost
Glenn and Dallery (2007)	Breath CO	Video recorded CO samples on a computer; emailed to study team	CO monitor, webcam, laptop	2×/day for 20 days	Adult smokers (n = 14)	NR	Feasible approach for remotely monitoring smoking and delivering incentives	Equipment was loaned to participants; drove to participant homes to set up
Stoops et al. (2009)	Breath CO	Video recorded CO samples; uploaded through a secure website (Motiv8)	CO monitor, home computer	2×/day (8 h apart) for 6 wks	Rural adult smokers (n = 68)	67%	Feasible approach for rural smokers	Participants required to have a home computer with Internet
Reynolds et al. (2008)	Breath CO	Video recorded CO samples; sent electronically to study staff	CO monitor, webcam, laptop	3×/day (5 h apart) for 30 days	Teen smokers, ages 14-17 (n = 4)	97%	Feasible approach for adolescent smokers	Small n
Meredith et al. (2011)	Breath CO	Video recorded CO samples; uploaded through a secure website (Motiv8)	CO monitor, webcam, laptop	2×/day (8 h apart) for 2 wks	Adult smokers (n = 13)	NR	Feasible to deliver incentives using group contingencies and provide support platform for participant communication with each other	Small n
Dallery et al. (2013)	Breath CO	Video recorded CO samples; uploaded through a secure website (Motiv8)	CO monitor, webcam, laptop (laptops loaned to 10% of participants)	2×/day during 28 day treatment phase; 2/wk during 21 day thinning phase	Adults smokers (N = 77)	NR	Feasible approach for remotely monitoring smoking and delivering incentives	Participants must be near computer to submit CO samples
Hertzberg et al. (2013)	Breath CO	Video-recorded CO samples on a smartphone	Breath CO monitor and smartphone (equipped with camera)	2×/day for 7 wks	Adult smokers with PTSD (N = 22)	93%	Feasible approach for mobile remote monitoring of smoking and delivering incentives	None noted
Meredith et al. (2014)	Breath CO	Mobile-phone based breath CO meter (prototype) in laboratory	Mobile CO meter, connection cord, smartphone (iPhone 4)	4 breath samples total in laboratory	60 adults (20 regular smokers, 20 light smokers, and 20 non-smokers)	NA	Breath CO was correlated with commercial meters; good acceptability of the mobile meter	CO monitor was a prototype and not currently commercially available
Ali et al. (2012)	Respiration measurements	Breathing via respiratory inductance plethysmograph	Respiratory inductance plethysmograph and Android mobile phone for data transfer	1) 13 observed smoking sessions; 2) 7 days in natural environment during waking hours	1) 10 adult smokers; 2) 4 adult smokers	NR	Developed models could detect puffs with 86.7% accuracy	False positives; validation required self-reported cigarettes in the natural environment
Sazonov et al. (2013)	Breathing patterns and arm movements	Breathing via respiratory inductance plethysomograph; Hand-to-mouth movement via wrist sensor	Personal Automatic Cigarette Tracker (PACT): respiratory inductance plethysmograph	Laboratory validation; Engaged in various activities including smoking a cigarette	Adult smokers (N = 20)	NA	Smoking resulted in unique breath patterns that were highly correlated with hand-to-mouth gestures; Promising for detecting smoking	Bulky system (vest, sensors, electronics); Must be validated through natural environment smoking and large datasets of continuously monitored activity

Table 1 (continued)

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Authors (Year)	Biomarker	Collection method	Hardware	Timing of data collection	Study sample	Adh.	Conclusions	Barriers or Challenges
Raiff et al. (2014)	Hand-to-mouth gestures	Hand-to-mouth gestures measures through kinematic sensors placed on the wrist, elbow, and shoulder	Shimmer kinematic sensors; data transmitted to an Android tablet	Laboratory validation; Six cigarettes measured per participant	Adult smokers (N = 4)	NA	Algorithms performed well in detecting smoking movements	Non-smoking movements towards the face present difficulties for analysis; Laboratory-based validation
Alcohol								
Alessi and Petry (2013)	Breath alcohol concentration (BrAC)	Video recorded BrAC samples, participant texted results	Alcohol breathalyzer; cellphone	1-3 prompts/day (avg 10 prompts/wk) for 4 wks	Adults frequent drinkers (N = 30)	89%	Feasible approach to deliver incentives contingent on alcohol abstinence remotely	Manual text prompts and reminders; only sampled until 11pm
Barnett et al. (2011)	Transdermal alcohol secretions	Readings from the Secure Continuous Remote Alcohol Monitoring (SCRAM) bracelet	SCRAM bracelet (electrochemical alcohol sensor); transferred to home modem then transferred to research staff via landline OR returned to clinic 3×/wk for data download	Readings automatically taken every 30 min; transmitted 1/xday for 3 wks	Adult heavy drinkers (N = 13)	NA	Feasible approach to dentifiedy monitor alcohol use to provide incentives remotely	Small n, brief intervention period, no randomization or control group, several false negatives, issues with technology acceptability
Illicit Substances								
Boyer et al. (2012)	Electrodermal activity, body motion, skin temperature, and (optionally) heart rate	Sensor band transmits physiological data to mobile phone, which triggers EMA assessments of mood and surroundings	Sensor band; mobile phone for transmitted data	NA	Adult veterans with co-occurring SUDs & PTSD (N = 7 in focus groups)	NA	Approach appears feasible for use with this population	Some acceptability issues identified with the wristband by focus groups
Carreiro et al. (2015)	Electrodermal activity, skin temperature, acceleration	Continuous recording via wearable sensors worn on inner wrist	Q sensor wristband outfitted with sensors	Emergency Dept (ED): before, during, and after IV opioid administration; Community field test (Field): 4 h	ED: adult pain patients with varying opiate use history (N = 4); Field: chronic cocaine user (N = 1)	NA	Biometric (EDA, temperature, acceleration) changes associated with IV opioid and cocaine use in controlled settings	Very low enrollment among eligible cocaine users due to potential participant concerns about privacy
Gambelunghe et al. (2013)	Sweat cocaine levels	Sweat-collection patches worn on the right or left forearm, back, or abdomen	Sweat-collection patches	Patches were worn in 7-day intervals for 2 wks (hair and urine samples also collected for comparison)	Treatment-involved adults with a history of cocaine abuse (N = 48) and drug-free healthy adult controls (N = 10)	94%	Results varied in cocaine detection; overall, sweat analysis may be a long-term, noninvasive drug monitoring solution	Drug concentrations from sweat analysis may be affected by physical activity, ambient temperatures, and environmental factors
Stress								
Gregoski et al. (2013)	Heart rate; Blood Pressure	Smartphone-based photoplethysmograph; ambulatory BP monitor	Smartphone (Android equipped with LED and camera); Spacelabs Healthcare ambulatory BP monitor	baseline, 2×/day prompts, 1-, 2-, 3-month follow-up	preEH male teachers (N = 3)	NR	Feasible to collect heart rate in trials for breathing awareness meditation for stress reduction	Small n
Lu et al. (2012)	Galvanic skin response (GSR), vocal acoustic features (pitch, rate)	GSR via wrist band; voice via built-in smartphone microphones	Affectiva wrist band, Android phone + waist microphone	4 + days of tasks in laboratory and standardized field location	Healthy young adults (N = 14)	N/A	Feasible to detect stress reactions through vocal features using built-in smartphone microphone in indoor and outdoor settings	Small n, proof-of-concept; constrained set of stress challenges limit generalizability conclusions; substantial computational and power drain on older model phones
Sun et al. (2012)					Healthy adults (N = 20)	N/A		

Study	Measure	Method	Device/Platform	Setting/Protocol	Sample	%	Findings	Limitations
	ECG, galvanic skin response (GSR)	Wireless ECG via sensor and chest strap; GSR sensor on fingers with wrist cuff	SHIMMER platform developed by Intel's Digital Health Group; transmitted to PC via Bluetooth	One laboratory visit — 3 (sit, stand, walk) x 2 (baseline, stress) design			Feasible to detect and classify mental stress based on few basic indicators of stress activity and movement	Small n, proof-of-concept; Unclear whether could be replicated in real-world environments (dentified as a next step)
Plarre et al. (2011)	ECG, skin conductance, skin temperature, ambient temperature, accelerometer, relative lung volume via respiratory inductive plethysmograph band	Wearable sensors; lab-based stress procedure and field-based EMA protocol	AutoSense wearable sensor suite; Bluetooth bridge that sends data to mobile phone	In lab, on multiple occasions during stress paradigm; in field test, 2 days, approximately 25 prompts/day	College students (N = 21)	NR	Respiration was highly discriminatory of physiological stress possible to calibrate stress-related measures to individuals	Data loss/corruption; interference from physical activity; need other types of data; dichotomous classification of stress; unclear how much time needed to calibrate to individual
Robles et al. (2011)	Salivary alpha amylase	Salivary test strips	Nipro sAA portable biosensor	At home, 3 ×/day, 2 days (low- and high-stress times during semester)	Healthy, male dental students			
(N = 54)	91%	Higher sAA was related to higher ratings of subjective distress.	Importance of clarifying timescale for self-reported distress (current, min, hrs) given high temporal sensitivity of sAA; consideration for timing and diurnal rhythms					
Robles et al. (2012)	Salivary alpha amylase	Salivary test strips	Nipro sAA portable biosensor	In clinical laboratory, 3 sessions on 3 visits (preop, surgical day, postsurgical follow-up), 4 sAA readings per visit	76 healthy participants, 64.5% female), 18–40 years, undergoing oral/maxillofacial surgery for extraction of molar	N/A	sAA levels were not elevated during surgery visit compared to consult and post-surgical visits, but higher sAA was associated with helplessness responses to pain.	Need for restrictions or at least assessments of eating and drinking for all assessments; need for additional individual difference data to account for variability in sAA readings
Anxiety								
Repetto et al. (2013)	Heart rate, electrodermal activity	Finger sensors wirelessly transmitted data to tablet	Wireless (Bluetooth) multi-sensor module, finger sensors for simultaneous measurement of HR and GSR	Varied by condition; 8 sessions, pre- post-	Treatment-seeking adults (age 18-50) with GAD at public health clinic (N = 25)	100%	Mobile exposure therapy via virtual reality was feasibly delivered with reductions in self-reported anxiety and heart rate; can incorporate biofeedback data; no group differences on outcomes with or without biofeedback	Small n, lab-based HR and GSR data; Clinic-based
Autism								
Rehg et al., 2013	Infant/toddler social and communicative behavior (social	Electrodermal activity through wearable sensors, video, and audio streams	Cameras, microphone, electrodermal activity and accelerometry sensors	Laboratory-validation study; 3–5 min adult-child interactive assessment	children (n = 121; ages 15–30 months)	NA	Methods are described for decoding the child-adult interactions	Complex behavior requires the integration of several data streams; this validation makes

Table 1 (*continued*)

Authors (Year)	Biomarker	Collection method	Hardware	Timing of data collection	Study sample	Adh.	Conclusions	Barriers or Challenges
	attention, back-and-forth interaction, nonverbal communication)						through multi-modal activity recognition	use of a specific semi-structured play interaction protocol (Rapid-ABC)
Ye et al., 2015	Instances of eye contact directed at adults from children	Glasses equipped with an outward-facing camera are worn by adults and capture video to detect instances of eye contact	Eye glasses with a high definition outward-facing camera (point of view camera; Pivothead)	Laboratory-based validation study	children (n = 12; ages 18-28 months)	NA	The method developed in this study to detect bids for eye contact outperformed other methods	Face detector as part of the system was not ideal as part of the adult-view video
Mood Disorders								
Gruenerbl et al., 2014	Mobility - physical motion and travel patterns (# locations visited, # hrs outside, distance traveled, etc.)	Passive, automatic capture of accelerometer and GPS data; phone-based questionnaires	Built-in smartphone inertial sensors and GPS	Continuous; 12 wk trial; data summarized daily	Adults with bipolar disorder (n = 12)	83% completed study	Feasible to gather mobility data in patients with bipolar disorder; promising classification accuracy for depressive and manic states	Establishing ground-truth standards; 2/12 participants reported no variation in mood state
Osmani et al., 2013	Activity level	Passively collected accelerometry data; user-reported mood, activity, sleep	Built-in smartphone accelerometer data sent wirelessly to server	Continuous collection; duration NR	Adults with bipolar disorder (n = 9)	NA	Feasible to collect passive accelerometry data in patients with bipolar disorder; activity data corresponded with state mood in most pts	Compliance with carrying phone; need for personalized predictive models
Saeb et al., 2015	Mobility, circadian movement, phone usage features, duration, frequency	GPS-derived location and movement data; phone use features; sent wirelessly to server	Mobile phone	Continuous over 2 weeks	Adults (n = 40)	100% completed the study; 70% provided >50% sensor data	Passively acquired GPS and phone usage data discriminated people with and without depressive symptoms	30% of participants had insufficient data due to connectivity and power drain issues; non-clinical sample

Note. Adh. = adherence. NR = not reported. NA = not applicable.

products are tested in scientifically rigorous pre-market studies. Depending on the type of biosensor and its intended use, Food and Drug Administration (FDA) regulations governing medical or investigational devices may pertain. These issues are complex, and communication gaps between academia and industry threaten to slow progress in this field. Moreover, it is important that experts across academic, clinical, and technical disciplines engage in meaningful partnerships throughout the development and evaluation phases of mHealth research. Such partnerships are often mutually beneficial, as clinicians, engineers, computer scientists, intended users, and other contributors bring unique expertise and perspectives to this work. *Recommendations:* Clinical researchers should partner with experts in a range of disciplines relevant to mHealth and the aims of their particular project. They should seek out consultation at the institutional or agency level, including with legal counsel when appropriate, to understand which of these issues pertain to their work. Many universities have offices dedicated to helping investigators navigate intellectual property, commercialization, and regulatory issues. It may also be useful to collaborate with business partners in all stages of the research process, including as members of the investigative team when appropriate. The catalog of available devices is also changing rapidly, but understanding institutional policies and protections can help to ensure that the technology is being used to its fullest potential while also protecting the interests of the investigator. These issues are complicated, especially when working with a multidisciplinary team, but such works is essential to innovation in mHealth research (Kumar et al., 2013b).

6.2.3. Protect the privacy and confidentiality of the participant

Important issues also exist around the privacy, confidentiality, and security of the sensitive data being collected through mHealth tools and through biomarker acquisition and analysis, especially in the psychiatry and substance use fields (Arora et al., 2014). For example, patients or participants in research studies may be concerned that biomarker data indicating recent use of illicit substances could be shared with the criminal justice system, employers, or other agencies. Data and security issues are a major concern for mHealth, specifically compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations and standards (Luxton et al., 2012). *Recommendations:* Researchers must work diligently with software programmers, server and networking experts, institutional review boards, legal consultants, security and privacy experts, and other regulatory bodies to ensure that participant data are confidential, de-identified when appropriate, secured and encrypted, and handled in an ethically responsible manner. Procedures to protect data must be transparent to participants; they should know exactly who will have access to these data and how they will be used and secured. These points pertain to all research but appear to be especially important to mHealth and remote data collection. A recent study found that privacy concerns with mHealth technology among consumers tended to be variable and context-specific (i.e., type of information, who sees information, for what purpose, etc.), and that having control over security features was important (Atienza et al., 2015). Because mobile devices can be used almost anywhere, researchers must also be sensitive to participants' comfort and privacy needs during sample collection—particularly when specimens such as saliva must be collected for measurements—while balancing the need for rigorous authentication and validation of participant identity and adherence to methodology (i.e., via facial or fingerprint recognition, video capture). User-guided input should be sought when developing research protocols involving mHealth strategies for biomarker measurement in advance of larger experiments to help identify and minimize barriers related to perceived invasiveness and privacy.

6.2.4. Assessing the user experience

Understanding the user experience is essential to knowing what is reasonable to ask of participants. Engagement and sustainable use of any technology system is critical for robust data collection efforts, yet response fatigue and barriers to continued engagement pose major concerns and challenges to the field in this area. Questions remain about user motivation, sustainability, efficacy, and generalizability of mHealth approaches. Some critics have noted that typical users of current mHealth tools—including people with favorable adherence to wearable sensors like Fitbits—are relatively healthy and well-resourced, limiting our understanding of whether such devices can be used optimally in people with psychiatric problems (Patel et al., 2015). *Recommendations:* Thorough, iterative acceptability testing of devices and assessment protocols among all stakeholders during development and implementation of mHealth technology cannot be overlooked. Acceptability testing through focus groups, interviews, and in small field studies is recommended to troubleshoot barriers and address participant burden before launching large-scale projects. These questions should be revisited as devices evolve. For instance, as smartphones and biosensors become more compact, with longer battery life, and more computing power, it may be possible to revise protocols to reduce participant burden. A user-centered approach requires investigators to be agile and willing to adjust methods in response to feedback, sometimes via iterative study designs that anticipate protocol modifications after a study has started (Kumar et al., 2013a). Additionally, the participant or patient must perceive some value for continuing to engage with the technology, and the content or purpose must be relevant to sustain engagement. Participants in research studies are often compensated for their time, but some may find enjoyment or gain insight from answering questions about their mood, stress levels, behavior, or tracking physiological functioning in a systematic fashion. It is essential to consider the burden placed on the individual and the value the individual perceives from his or her effort. Passive data collection systems from unobtrusive sources may be ideal for sustained use. Response fatigue may be less likely to occur when response effort is low.

6.2.5. Justify costs

Initial research and development of technology integration can be a large expense, particularly when new biosensor devices and processing tools are first released. There are costs associated with the purchase and maintenance of devices, data collection and management infrastructure, and accompanying materials (e.g., test strips). The use of mHealth technologies for remote biomarker, behavior, and symptom measurement should demonstrate clear scientific and economic advantage over traditional methods to be implemented widely. Complicated biosensing systems or frequent, multi-step assessment procedures may not be realistic or cost efficient for long-term use, but could be of great importance in research settings or in assessment or acute clinical care, such as during particularly severe episodes or transition between levels of care. *Recommendations:* Adding economic analyses within research trials using remote biosensors versus conventional approaches will be important to assess savings. Health economists can be consulted to aid in thorough cost-effectiveness studies to justify the use of potentially expensive research equipment and to examine feasibility of translating similar methods to clinical settings (see Table 1).

7. Conclusions

The future of mHealth tools and methods in psychiatric research is bright. Strides in this field will emerge through synergistic, multidisciplinary collaborations among engineers, computer scientists, informaticians, clinical scientists, health care professionals, regulatory experts, user experience teams, and end-users themselves. Research and service funding institutions increasingly recognize the value of mHealth approaches and have prioritized training and multidisciplinary research in this area through collaborations and initiatives within and across agencies (Nilsen et al., 2012; Nilsen et al., 2013). The recently announced Precision Medicine initiative outlined by The White House and backed by the NIH emphasizes an approach to treating and preventing disease that is tailored to the individual (Collins and Varmus, 2015; Office of the Press Secretary, January 30, 2015). This initiative will rely on detailed and integrated data for the individual patient, collected and analyzed frequently via remote sensors. These devices will continue to evolve and become less expensive, less obtrusive, and more sophisticated with respect to the range of biomarkers they can collect remotely, accurately, quickly, and unobtrusively. Such technologies hold great promise toward advancing understanding and clinical care of psychiatric problems.

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Contributors

Drs. Adams and McClure developed the initial concept for this manuscript, conducted the literature review, and wrote the manuscript. Drs. Gray, Danielson, Ruggiero, and Treiber contributed to the conceptualization of the study, offered substantive feedback on iterative versions of the manuscript, and assisted with editing the paper. All authors approved have approved the final manuscript.

Disclosures

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